for each scheme and the numbers of patients attending for review at the end of the evaluation (the outcome measure used). Shared care had more patients attending for review at a slightly higher average cost per review. Average analysis may lead purchasers to think that the extra benefits of shared care can be obtained for £28.72 per patient. However, the key information required by purchasers is the additional cost per extra review achieved by shared care, not the average cost. From table 2 it can be seen that nurse practitioner care achieved a 75% review completion rate compared with 82% for shared care. The key benefit is the extra 7% of completed reviews achieved by shared care and comparing these with its extra costs. Hence the benefit of shared care is 18 extra patients reviewed for an extra cost of £976. Therefore the marginal cost effectiveness of shared care is £54 per extra reviewed patient, not £28.72.

Comment

In these two examples of economic evaluations we can see how the production and use of average cost and benefit data can mislead decision makers. Estimates of marginal costs and benefits are always preferable to average costs and benefits, and this has been advocated for several decades.[4,5] Despite this, there are often large evaluation costs incurred by calculating marginal rather than average values,[6] and in some cases this may justify using average costs. Indeed, health economists recognise the cost of collecting marginal cost information, and solutions, such as reduced datasets, have been proposed.[6] In addition, sometimes coincidentally, average costs may equate to marginal costs. Nevertheless, the temptation to use average costs and benefits should be avoided whenever possible.

This note shows that if more care is taken in the economic analysis marginal values may often be derived with little or no extra research effort. Even when marginal costs and benefits are more difficult to estimate, the improved precision of the evaluation may justify the increased research effort. For example, if average costs had been used when evaluating an early discharge scheme for patients with hip fractures they would have overstated its financial benefit by 200%.[7] For evaluations of competing interventions to produce valid results marginal costs and benefits should be used—not averages.

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Lesson of the Week

Nephrotic syndrome in childhood complicated by life threatening pulmonary oedema

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Beware of infusing too much 20% albumin too quickly in children with nephrotic syndrome

A consensus statement on nephrotic syndrome from the British Association for Paediatric Nephrology has recently recommended intravenous 20% albumin for the management of hypovolaemia in this condition.[1] The suggested dose is 1 g/kg over one to two hours followed by frusemide. Caution is required with this treatment, however, as considerable fluid shift may occur.[2] We describe three children who were transferred to our paediatric intensive care unit because they had developed life threatening fluid overload and pulmonary oedema after receiving an excessive dose or too rapid infusion of 20% albumin.

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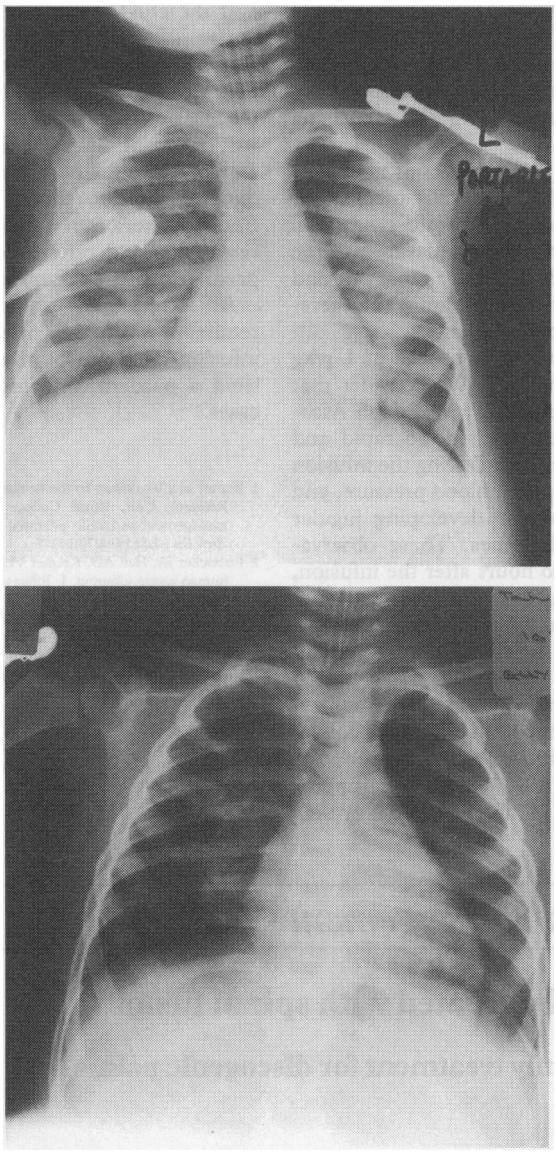
Case 1

A 4 year old girl presented to her local hospital with a 10 day history of periorbital and lower limb oedema, a three day history of diarrhoea and vomiting, and oliguria for the past 24 hours. Urine analysis showed heavy proteinuria. The plasma albumin concentration was 15 g/l, urea concentration 11·6 mmol/l, creatinine concentration 41 μmol/l, haemoglobin concentration 120 g/l, and urinary sodium concentration 11 mmol/l. Nephrotic syndrome was diagnosed, and oral prednisolone was started. Oliguria persisted and her weight increased. There was no response to intravenous frusemide. She was given 20% albumin at a dose of 3·5 g/kg ideal body weight over four hours. During the infusion she became breathless, cyanosed, and had a generalised seizure followed by respiratory arrest. At intubation pink frothy sputum welled from the trachea. Initial arterial blood gas tensions when she was ventilated with 100% oxygen were pH 6·87, P_{CO_2} 8·7 kPa, P_{O_2} 5·9 kPa, base excess −24·6. Central venous pressure was +20 cm H_2O. A chest *x* ray film showed severe bilateral pulmonary oedema (fig 1a). Immediate further management included venesection of 10 ml/kg, intravenous frusemide, and dopamine. After her transfer to the paediatric intensive care unit continuous venovenous haemofiltration was started. The pulmonary oedema improved within 24 hours (fig 1b). Renal failure was managed by continuous venovenous haemodiafiltration. Doppler ultrasonography showed patent renal veins and good arterial flow. Corticosteroid treatment was continued, and after her renal function recovered she went into remission.

Case 2

A 17 month old boy, admitted to his local hospital with generalised oedema, was found to have nephrotic syndrome. Oral prednisolone was started. Oedema and weight gain worsened, and he was given intravenous



Case 1: Severe pulmonary oedema on chest radiology after emergency intubation (top) *resolution of pulmonary oedema after 24 hours' ventilation and haemofiltration* (bottom)

20% albumin at a dose of 2·6 g/kg ideal body weight over three hours, without frusemide. Respiratory failure developed requiring ventilation, and he was given frusemide and transferred to our paediatric intensive care unit. Hypoxia persisted despite high pressure ventilation with 100% oxygen. Blood pressure was 120/88 mm Hg and central venous pressure was 11 cm H_2O. Chest *x* ray films showed pulmonary oedema. Ventilation was required for five days. He went into remission from nephrotic syndrome after 16 days of treatment with prednisolone.

Case 3

A 15 month old girl with sickle cell disease was admitted to her local hospital with a one week history of generalised oedema and ascites. Initial assessment showed proteinuria and a plasma albumin concentration of 13 g/l. Oral prednisolone was started. Oedema and ascites worsened, and 20% albumin was given at 1 g/kg ideal body weight over one hour. There was no diuretic response to frusemide 1 mg/kg, and she developed respiratory distress, requiring ventilation and transfer to our paediatric intensive care unit. On arrival blood pressure was 96/50 mm Hg and central venous pressure was 13 cm H_2O. A chest *x* ray film showed pulmonary oedema, but the radiological changes improved over 24 hours with frusemide and ventilation. Further cautious infusions of 20% albumin were given for recurrent hypovolaemia, and remission occurred 22 days from the start of prednisolone treatment.

Discussion

Early reports of treatment with concentrated human albumin showed rapid expansion in plasma volume; hypertension, tachycardia, and dyspnoea were seen in some patients.[2] Acute, transient hypertension occurred in 10 of 24 children with severe nephrotic oedema receiving 25% albumin infusions of 1 g/kg over 30 to 60 minutes.[3] The International Study of Kidney Disease in Children, into deaths from minimal change nephrotic syndrome, described one death from cardiorespiratory arrest after salt poor albumin infusion.[4] More recently, the use of 35 treatment courses of albumin and diuretic treatment in 21 children with nephrotic oedema was studied retrospectively.[5] A mean dose of 0·9 g/kg of albumin was infused over one to four hours, with intravenous frusemide given during or within 60 minutes of completion of the infusion. Acute hypertension occurred in 46% of treatment courses and acute respiratory distress in 11%. One child developed acute congestive cardiac failure, and one required ventilation for respiratory failure. The authors were unable to identify risk factors, such as response to previous albumin infusions, that predicted these complications.

In cases 1 and 2 we believe an excessive dose of albumin was infused (3·5 g/kg and 2·6 g/kg, respectively). In case 3, 1 g/kg was given over only one hour. The dose and rate of albumin infusion are not the only considerations. The child with oedema and severe hypovolaemia must be distinguished from the child who is oedematous but not hypovolaemic, as the aim of treatment with 20% albumin differs in these two situations.

In hypovolaemia 20% albumin infusions increase the circulating blood volume and systemic perfusion. In the normovolaemic child with incapacitating oedema albumin promotes a shift of fluid into the intravascular space and, with frusemide, a diuresis. In the hypovolaemic child inappropriate use of frusemide may worsen the hypovolaemia. Clinical and laboratory assessment of intravascular volume are therefore essential.

Symptoms, signs, and investigations in hypovolaemia are shown in the box. Toe temperature, determined by a cutaneous probe, is a simple guide to

Clinical features of hypovolaemia

Symptoms

- Abdominal pain
- Anorexia
- Vomiting

Signs

- Tachycardia
- Hypertension or normotension, rarely hypotension
- Poorly perfused limb extremities
- Core toe temperature difference >3°C
- Oliguria

Investigations

- Raised haemoglobin concentration or haemocrit
- Raised plasma urea, with relatively normal plasma creatinine
- Urinary sodium <5 mmol/l (unreliable if diuretics given previously)

peripheral perfusion. It is important to appreciate that the blood pressure may be normal or raised in the presence of severe hypovolaemia in these children—because of increased plasma renin concentrations produced by renal ischaemia and increased plasma vasopressin concentrations.[6]

There is debate over the pathogenesis of nephrotic oedema.[7] It is thought that the "underfill" mechanism is more common in childhood nephrotic syndrome. Hypoalbuminaemia leads to reduced plasma oncotic pressure, hypovolaemia, and secondary renal salt and water retention. Infusions of 20% albumin are therefore appropriate in hypovolaemic patients.

We recommend 20% albumin at a dose of 1 g/kg ideal body weight over four hours. We consider that one to two hours, recommended by the British Association for Paediatric Nephrology,[1] is too rapid and increases the risk of fluid overload. During the infusion it is essential to monitor the pulse, blood pressure, and respiratory rate and to look for developing jugular venous engorgement and dyspnoea. These observations should continue for two hours after the infusion, as fluid shift may continue. Blood pressure may actually fall to a more normal level.[7] Frusemide should not be given while clinical assessment continues to suggest hypovolaemia.

Occasionally nephrotic syndrome may lead to profound hypovolaemia and shock. Rapid expansion of the intravascular volume with 4·5% human albumin solution 10-20 ml/kg over 30-60 minutes is appropriate. Subsequent infusions of 20% albumin may then also be needed.

If the child is assessed as normovolaemic and has severe symptomatic oedema we recommend 20% albumin at a dose of 1 g/kg ideal body weight over four hours, with frusemide 1 mg/kg given two hours into the infusions.

If signs of fluid overload do develop, frusemide 1 mg/kg should be given intravenously. If this produces no improvement 5 mg/kg should be given. Further deterioration may necessitate venesection and ventilation and referral to a centre with facilities for paediatric intensive care and haemofiltration.

As intravascular volume may change daily until remission occurs it must be assessed before each infusion of 20% albumin. Advice over the telephone from a paediatric nephrologist may help in difficult cases.

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Controversies in Management

Should backache be treated with spinal fusion?

Spinal fusion is the only treatment for discogenic pain

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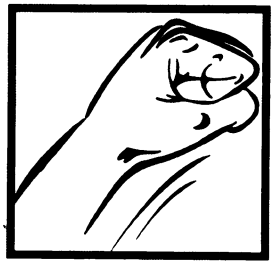

Backache indicates pain originating in the vertebral column (most commonly in the lowest two mobile segments of the lumbar spine). It is felt mainly in the lower back and buttocks, often being referred to the lower limbs. Referred pain in the limb can be confused with radicular pain (sciatica) from nerve root compression.

Fusion is a non-specific term. It comes from the Latin *fundere*—to pour or to melt. In the context of the spine, fusion entails welding or stiffening two or more vertebral bodies. Arthrodesis might therefore be a more appropriate word (removing of the articular surfaces and securing bony union[1]).

History

Hippocrates in 380 BC observed spontaneous fusion of the facet joints in a case of spinal tuberculosis. It was nature's attempt to halt the progress of the deformity. Hibbs read the work of Hippocrates, and in 1911 surgically fused the posterior spinal elements in young patients with spinal tuberculosis.[2] This successfully prevented subsequent deformity. Later Hodgson and Stock used anterior spinal fusion for tuberculosis and then the correction and fusion of scoliosis[3]; this became standard surgical treatment for these problems.

Fusion today

Today fusion is an important part of the conventional surgical management of spinal tumour, deformity, and infection as well as trauma resulting in an unstable compression fracture visible in an *x* ray film. The role of fusion is questioned, however, when trauma produces a symptomatic tear of the annulus not visible in an *x* ray film.

There are few published descriptions of the rationale for fusion of the lumbar spine, but consider the following two:

Firstly, movement of a motion segment is painful. Therefore elimination of that motion between vertebrae should eliminate the pain.[4] Depending on the preference and training of the surgeon, the fusion may be performed through the facet joints or between the vertebral bodies (the latter is mechanically preferable), between the laminae (obsolete), or between the transverse processes (traditional).

Secondly, pain is shown by discography to be due to a torn annulus—so-called discogenic pain. Removal of the annulus is a logical clinical decision, optimally through an anterior approach. But the spine is clearly destabilised by this disc clearance. A bone graft to replace the disc by filling the defect and maintaining the height of the disc space is therefore appropriate and logical.

Why use fusion?

The controversy surrounds primary fusion for backache. The indication for fusion is generally agreed for spondylolisthesis or postsurgical instability after extensive laminectomy.

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